Reframing the Retina Pipeline

By moving beyond thinking of the pipeline as which drug is in which phase, we can take a fresh perspective on therapeutic candidates in development.

BY PRAVIN U. DUGEL, MD

It is tempting to observe the retina therapeutics and pharmacology pipeline the way we watch a horse race—which company is ahead of the pack, which ones are falling behind, and which ones are surging in the sprint toward the finish line (in this metaphor, regulatory approval).

But by thinking only in terms of which drugs are in which research phases, we rob ourselves of the opportunity to understand them from other perspectives. I suggest that we consider drug candidates not by whether they are in phase 1, 2, or 3, but by their class, molecular size, and potential level of disruption.

Of course, trial designs and results are important. But consider the frameworks I use in each section below.

COMBINATION THERAPY

We often think of therapeutic options as binary—either this drug or that drug will show better efficacy. However, some drugs working together may deliver a one-two punch that could result in a greater therapeutic response. I submit the following examples.

Faricimab

Faricimab (Genentech/Roche) is a bispecific monoclonal antibody that neutralizes VEGF-A and angiopoietin-2. It is designed to have fast systemic clearance and a minimal inflammatory response.

We know the importance of VEGF-A inhibition in wet age-related macular degeneration (AMD) and diabetic macular edema (DME). Some clinicians may be less familiar with the importance of inhibiting angiopoietin-2. Angiopoietin-2 binds to the Tie2 receptor on the cell surface, resulting in destabilization of endothelium and the destruction of pericytes. As a result, exudation and fluid leakage occur, as does an upregulation of inflammatory cytokines. Additionally, angiopoietin-2 upregulates VEGF-A.

Simultaneous inhibition of VEGF-A and angiopoietin-2 could be key to improving outcomes for patients with wet AMD and DME. To find out if this is the case, a series of phase 2 studies have been initiated.

The BOULEVARD study enrolled 229 patients with DME.[1] Patients who received 6.0 mg faricimab demonstrated a statistically significant gain of 3.6 letters compared with patients who received 0.3 mg ranibizumab (Lucentis, Genentech; $P = .03$). "These findings suggest the benefit of simultaneous inhibition of angiopoietin-2 and VEGF-A with faricimab for patients with DME," the study authors wrote.

The AVENUE[2] and STAIRWAY[3] trials were designed to evaluate faricimab in patients with wet AMD. AVENUE was a 36-week study with five arms. Patients were randomly assigned to monthly therapy of 0.5 mg ranibizumab, 1.5 mg faricimab, or 6.0 mg faricimab; or to 6.0 mg faricimab monthly for 3 months and then 6.0 mg every 8 weeks; or 0.5 mg ranibizumab monthly and then 6.0 mg faricimab monthly. The faricimab-treated patients achieved meaningful vision gains and reductions in central subfield thickness.[4]

The STAIRWAY trial randomly assigned patients to receive 6.0 mg faricimab every 12 weeks after 3 monthly loading doses, every 16 weeks after 3 monthly loading doses, or monthly 0.5 mg ranibizumab. Of 55 faricimab-treated patients, 36 patients (65%) had no active disease 12 weeks after the final loading dose. At 52 weeks, BCVA gains in all three groups were similar, suggesting that combination therapy with faricimab every 12 or 16 weeks was as effective for improving vision as monthly ranibizumab therapy.[5]

The phase 3 trials TENAYA and LUCERNE will compare 6.0 mg faricimab every 16 weeks against 2.0 mg aflibercept (Eylea, Regeneron) every 8 weeks.[6,7] Both studies are enrolling patients.

OPT-302

OPT-302 (Opthea) is a soluble fusion protein comprising extracellular domains 1–3 from VEGF receptor 3 combined with a human Fc-fusion protein. The compound binds to VEGF-C and VEGF-D, which promote blood and lymphatic vessel development.

These targets are different from those of ranibizumab and bevacizumab (Avastin, Genentech), which bind to VEGF-A, and of aflibercept, which binds to VEGF-A, VEGF-B, and placental growth factor. OPT-302 is being investigated as an adjunctive anti-VEGF therapy. The theory is that, as VEGF-A inhibition drives upregulation of VEGF-C and VEGF-D,[8,9] the addition of OPT-302 in patients already undergoing anti-VEGF therapy may result in greater efficacy.

No adverse safety profile was

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observed in a phase 1/2a study of OPT-302.[10] In a phase 2b study, the compound met the primary endpoint of superiority in mean VA gain at 24 weeks compared with ranibizumab monotherapy in treatment-naïve patients with wet AMD.[11]

The concept of adjunctive therapy with OPT-302 should be encouraging to those who believe that combination therapy is part of the future of retina. By building upon the success of anti-VEGF therapy—and helping to address the upregulation of VEGF-C and VEGF-D secondary to anti-VEGF therapy—this adjunctive therapy may improve the efficacy of the agents now in use.

CONSIDERING MOLECULAR SIZE

Brolucizumab (Beovu, Novartis) is the smallest anti–VEGF A molecule approved by the US FDA. The drug, which was approved in October for the treatment of wet AMD, is a humanized single-chain variable fragment with a molecular weight of approximately 26 kDa and a half-life of 5.6 days. By comparison, aflibercept is approximately 97 to 115 kDa and ranibizumab is approximately 48 kDa. The molar dose of brolucizumab is 11.2 to 13.3 times higher than that of aflibercept.

KSI-301 (Kodiak Bioscience), on the other hand, is a large molecule. KSI-301 is an antibody-biopolymer conjugate consisting of an antibody with an inert immune effector function joined with an optically clear phosphorylcholine biopolymer with a high molecular weight. The drug is delivered intravitreally and is designed to exhibit durability in the eye but rapid systemic clearance.

The high molecular weight of KSI-301 may provide an important dosing advantage. At 3 months, KSI-301 could provide an ocular concentration 1 million times greater than ranibizumab, 100,000 times greater than brolucizumab, and 10,000 times greater than aflibercept.

The phase 2 DAZZLE study will enroll 400 treatment-naïve patients with wet AMD.[12] Patients will be randomly assigned to receive 5 mg KSI-301 every 12 or 16 weeks after 3 monthly loading doses or 2 mg aflibercept every 8 weeks after 3 monthly loading doses.

Molecular size is not a driving factor of success in and of itself—that is, molecules aren't safer or more effective just because of their size. Still, it's important to point out that our field is taking two very different approaches to molecule design, both of which may result in improved efficacy over existing therapeutic options.

COMPANIES TO KEEP AN EYE ON

A number of companies have drugs in the retina pipeline that may eventually receive regulatory approval. Here are five companies with the potential to be disruptive players.

Oxurion

The pipeline of Oxurion (formerly known as ThromboGenics) includes THR-149, a plasma kallikrein inhibitor designed to treat DME. In a phase 1 open-label multicenter nonrandomized trial evaluating the safety of a single injection of THR-149, investigators found no dose-limiting toxicity or any drug-related serious adverse events.[13] THR-149 was given only once in the study, and improvement 6.5 letters of BCVA was seen at day 90.

Further clinical research is warranted to understand the potential of THR-149 as a long-duration treatment option.

PanOptica

PAN-90806 (PanOptica) is a topical formulation of a small-molecule tyrosine kinase inhibitor (TKI) for the treatment of wet AMD. In a phase 1/2 dose-ranging clinical trial, more than half of patients receiving once-daily PAN-90806 for 12 weeks completed the study without needing rescue therapy with an anti-VEGF agent.[14] Of the 51 patients in the study, 88% experienced clinical improvement or stability of their disease.

Nine patients (17.6%) experienced at least one drug-related adverse event, five (9.8%) of which were related to the cornea. Of the three patients who discontinued use of the drug, two of them did so for a drug-related reason. No serious adverse events were observed.

Researchers have tried before to develop an eye drop for wet AMD treatment. More research is needed before we know whether PAN-90806 can succeed where others have not.

Graybug Vision

GB-102 (Graybug Vision), another TKI in the pipeline, is a microparticle depot formulation of sunitinib malate. The presence of TKI agents GB-102 and PAN-90806 in the pipeline is yet another example of how researchers are expanding beyond the anti-VEGF paradigm that defined medical retina

therapy for the past decade.

The phase 1/2a study ADAGIO assessed safety and tolerability of GB-102 in 32 patients with wet AMD.[15] Patients were randomly assigned to dosage arms of 0.25 mg, 0.5 mg, 1.0 mg, or 2.0 mg; there were eight patients in each arm. Each patient received a single intravitreal injection of GB-102, and the study group was followed for 8 months.

The study met its primary endpoints of safety and tolerability without dose-limited toxicity. Depending on the dosages, 50% to 88% of patients required no intravitreal injections of any anti-VEGF agent for 6 months after a single administration of GB-102.

Migration of bioabsorbable particles into the anterior chamber was observed in nine patients in the study. The events were self-limited, reversible, and showed no long-term sequelae at 6 months. A new manufacturing process intended to eliminate particle dispersion will be used in a phase 2b study.

The phase 2b ALTISSIMO study, which will evaluate GB-102 in patients with wet AMD, was initiated in October.[16,17] The study will enroll 160 patients who will be randomly assigned to receive 1 mg GB-102 every 6 months, 2 mg GB-102 every 6 months, or 2 mg aflibercept every 2 months.

Research on GB-102 is expanding beyond wet AMD therapy. A forthcoming phase 2a study will evaluate GB-102 in patients with DME and retinal vein occlusion.

Chengdu Kanghong Biotech

Conbercept (Chengdu Kanghong Biotech), a novel recombinant fusion protein, is designed to target VEGF-A, VEGF-B, and placental growth factor. The molecule includes the R2 domain 4, which increases the binding capacity of conbercept to VEGF.[18]

In the phase 3 PHOENIX trial, patients with wet AMD were randomly assigned to receive three monthly loading doses of conbercept 0.5 mg followed by quarterly treatment until month 12, or three monthly loading doses of sham injections followed by three monthly injections of conbercept 0.5 mg followed by three quarterly injections.[19]

A quarterly dosing schedule with conbercept 0.5 mg was effective at maintaining VA gains. At month 3, conbercept was superior to sham (+9.2 letters vs +2.0 letters, $P < .001$). At 12 months, mean improvement from baseline was approximately 10 letters in the conbercept group and 8.8 letters in the sham-to-treatment group ($P = .64$).

The PHOENIX trial was based in China; the PANDA-2 study is based in the United States.[20] PANDA-2 is a double-masked, parallel-group, randomized clinical trial that will evaluate the efficacy and safety of conbercept 0.5 mg, conbercept 1.0 mg, and aflibercept 2.0 mg for the treatment of wet AMD. More than 1,100 patients will be enrolled and will be treated for 92 weeks.

The drug, if approved, may join brolucizumab as a major disrupter of the anti-VEGF treatment landscape.

Allergan

It might seem funny to think of Allergan as a company to keep an eye on—after all, they have been a player in the retina space ever since the approval of the dexamethasone intravitreal implant 0.7 mg (Ozurdex, Allergan) in 2009. However, given the development of abicipar pegol (Allergan), it is worth considering the company's potential for disruption of the wet AMD paradigm.

Abicipar is a *designed ankyrin repeat protein*, or *DARPin*, therapy. DARPins are recombinant proteins derived from natural ankyrin proteins that consist of at least three (and usually four or five) repeat motifs.

In the phase 3 CEDAR and SEQUOIA studies, patients with wet AMD who were randomly assigned to receive abicipar 2 mg were dosed either every 8 weeks after three monthly loading doses or every 12 weeks after two monthly loading doses and a loading dose at week 12; other patients were randomly assigned to a monthly ranibizumab arm.[21,22]

Both studies' primary endpoint was the proportion of patients with stable vision at week 52. Stable vision was defined as a loss of less than 15 ETDRS letters from baseline. Both studies reached their primary endpoint, and quarterly abicipar treatment was shown to be noninferior to monthly ranibizumab therapy.[23]

The treatment schedules in CEDAR and SEQUOIA were unique. Abicipar is the only anti–VEGF-A agent to be effective in a phase 3 trial with a modified loading dose phase and dosing every 12 weeks. It remains to be seen what this means for real-world treatment and labeling.

An intraocular inflammation rate of approximately 15% was seen in both CEDAR and SEQUOIA. The MAPLE study was initiated to assess safety of abicipar produced via a new manufacturing process. According to a company press release, the rate of intraocular inflammation in MAPLE was 8.9%, and cases of inflammation were classified as mild to moderate.[24]

The FDA accepted a biologics license application for abicipar for the treatment of wet AMD in September, and the European Medicines Agency validated a marketing authorization application.[25] Action is expected from both agencies in the second half of 2020.

CONCLUSION

Keeping an eye on the retina pipeline can be useful for clinicians who want to participate in research. Those who want to stay abreast of the latest developments should attend late-breaking sessions at upcoming meetings and visit news sites such as Eyewire. ■

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PRAVIN U. DUGEL, MD
- Managing Partner, Retinal Consultants of Arizona, Phoenix
- Clinical Professor, USC Roski Eye Institute, Keck School of Medicine, University of Southern California, Los Angeles
- Physician Executive Director, Banner Eye Institute, Phoenix
- Editorial Advisory Board Member, *Retina Today*
- pdugel@gmail.com
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